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09/381,480	12/10/1999	MARK CHEE	018547-03053	4017

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EXAMINER	
CHAKRABARTI, ARUN K	
ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 03/25/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/381,480	Chee
Examiner	**Art Unit**
Arun Chakrabarti	1634

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Mar 4, 2003* .

2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-15* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-15* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Detailed Action*

Application/Control Number: 09/381,480

Art Unit: 1634

DETAILED ACTION

Claim Rejections - 35 USC § 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. Claims 1-2, 5-6 and 15 are rejected under 35 U.S.C. 103 (a) over Skiena (U.S. Patent 5,683,881) (November 4, 1997) in view of Futreal et al. (U.S. Patent 6,045,997) (April 4, 2000) further in view of Cantor et al. (U.S. Patent 5,795,714) (August 18, 1998).

Skiena teaches a method of analyzing a target nucleic acid (abstract), comprising:

a) designing an array of probes comprising a probe set comprising probes complementary to a reference sequence (Abstract, Table 1 and Column 2, lines 20-27 and Claim 1a);

b) hybridizing the target nucleic acid to the array of probes (Claim 1b);

c) determining the relative hybridization of the probes to the target nucleic acid (Claim 1c);

d) estimating the sequence of the target nucleic acid from the relative hybridization of the probe (Claim 1c and 1d);

e) providing a further array of probes comprising a probe set comprising probes complementary to the estimated sequence of the target nucleic acid (Claim 1d and 1e);

f) hybridizing the target nucleic acid to the further array of probes (Claim 1g);

g) determining the relative hybridization of the probes to the target nucleic acid (Claim 1g);

h) reestimating the sequence of the target nucleic acid from the relative hybridization of the probes (Claim 1h and Claim 2).

Skiena teaches a method further comprising repeating steps (e)-(h) as necessary until the reestimated sequence of the target nucleic acid is constant between successive cycles (Claim 2).

Skiena teaches a method of analyzing a target nucleic acid by designing an array of probes to be complementary to an estimated sequence of the target nucleic acid (Figures 2-3 and Claims 3-14).

Skiena does not teach the array of probes wherein the sequence of the target nucleic acid is a variant of the reference sequence.

Futreal et al. teach the array of probes wherein the sequence of the target nucleic acid is a variant of the reference sequence (Abstract, Figures 1, 2 and 4 and Column 10, lines 23-37).

Skiena does not teach a method wherein the target nucleic acid shows 50-99% sequence identity with the reference sequence.

Futreal et al. teach a method wherein the target nucleic acid shows 50-99% sequence identity with the reference sequence. (Figures 1, 2 and 4).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine and substitute the array of probes wherein the sequence of the target nucleic acid is a variant of the reference sequence of Futreal et al. in the method of Skiena since Futreal et al. state, "Such oligonucleotide probes or primers, as well as the full length sequence (and alleles, variants and derivatives) are also useful in screening a test sample

containing a nucleic acid for the presence of alleles and variants, especially those that confer susceptibility or predisposition to cancers, the probes hybridizing with a target sequence from a sample obtained from the individual being tested. The conditions of the hybridization can be controlled to minimize non-specific binding, and preferably stringent to moderately stringent hybridization conditions are preferred. The skilled person is readily able to design such probes, label them and devise suitable conditions for hybridization reactions, assisted by textbooks such as Sambrook et al and ausubel et al. As well as determining the presence of polymorphisms or mutations in the BRCA2 sequence, the probes may also be used to determine whether mRNA encoding BRCA2 is present in a cell or tissue (Column 9, lines 4-21)." An ordinary practitioner would have been motivated to combine and substitute the array of probes wherein the sequence of the target nucleic acid is a variant of the reference sequence of Futreal et al. in the method of Skiena in order to achieve the express advantages noted by Futreal et al. of probes which skilled person is readily able to design, label them and devise suitable conditions for hybridization reactions, assisted by textbooks such as Sambrook et al and ausubel et al., and which oligonucleotide probes or primers, as well as the full length sequence (and alleles, variants and derivatives) are also useful in screening a test sample containing a nucleic acid for the presence of alleles and variants, especially those that confer susceptibility or predisposition to cancers, the probes hybridizing with a target sequence from a sample obtained from the individual being tested.

Skiena in view of Futreal et al do not teach a probe array, which does not contain every possible probe sequence of a given length.

Cantor et al. teach a probe array, which does not contain every possible probe sequence of a given length (Column 13, lines 23-32).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine and substitute a probe array, which does not contain every possible probe sequence of a given length of Cantor et al. in the method of Skiena in view of Futreal et al., since Cantor et al. state, "In certain applications, an entire array of every possible sequence is not necessary and incomplete arrays are acceptable for use. For example, incomplete arrays may be utilized for screening procedures of very rare target nucleic acids where nonspecific hybridization is not expected to be problematic. Further, every member of an array may not be needed when detecting or sequencing smaller nucleic acids where the chance of requiring certain combinations of nucleotides is so low as to be practically nonexistent (Column 13, lines 23-32) ." An ordinary practitioner would have been motivated to combine and substitute a probe array, which does not contain every possible probe sequence of a given length of Cantor et al. in the method of Skiena in view of Futreal et al., in order to achieve the express advantages , as noted by Cantor et al., of incomplete arrays that may be utilized for screening procedures of very rare target nucleic acids where nonspecific hybridization is not expected to be problematic wherein every member of an array may not be needed when detecting or sequencing smaller nucleic acids where the chance of requiring certain combinations of nucleotides is so low as to be practically nonexistent.

3. Claims 7-14 are rejected under 35 U.S.C. 103 (a) over Skiena (U.S. Patent 5,683,881) (November 4, 1997) in view of Futreal et al. (U.S. Patent 6,045,997) (April 4, 2000) further in view of Cantor et al. (U.S. Patent 5,795,714) (August 18, 1998) further in view of Cronin et al. (U.S. Patent 6,027,880) (February 22, 2000)

Skiena in view of Futreal et al. further in view of Cantor et al. teach methods of claims 1-2, 5-6 and 15 as described above.

Skiena in view of Futreal et al. further in view of Cantor et al. do not teach a method wherein the reference sequence is 10 Kb nucleotides long, the array comprises a probe set comprising overlapping probes that are perfectly complementary to and span the reference sequence, and the further array comprises probes that are perfectly complementary to and span the estimated sequence.

Cronin et al. teach a method wherein the reference sequence is 10 Kb nucleotides long, the array comprises a probe set comprising overlapping probes that are perfectly complementary to and span the reference sequence, and the further array comprises probes that are perfectly complementary to and span the estimated sequence (Table 3, columns 63 and 64, Mutation Number 3849).

Skiena in view of Futreal et al. further in view of Cantor et al. do not teach a method wherein the reference sequence includes at least 90% of the human genome.

Cronin et al. teach a method wherein the reference sequence includes at least 90% of the human genome (Column 42, lines 15-25).

Skiena in view of Futreal et al. further in view of Cantor et al. do not teach a method wherein the array of probes comprises:

(1) a first probe set comprising a plurality of probes, each probe comprising a segment of at least six nucleotides exactly complementary to a subsequence of the reference sequence, the segment including at least one interrogation position complementary to a corresponding nucleotide in the reference sequence;

(2) second, third and fourth probe sets, each comprising a corresponding probe for each probe in the first probe set, the probes in the second, third and fourth probe sets being identical to a sequence comprising the corresponding probe from the first probe set or a subsequence of at

least six nucleotides thereof that includes the at least one interrogation position, except that the at least one interrogation position is occupied by a different nucleotide in each of the four corresponding probes from the four probe sets.

Cronin et al. teach a method wherein the array of probes comprises:

(1) a first probe set comprising a plurality of probes, each probe comprising a segment of at least six nucleotides exactly complementary to a subsequence of the reference sequence, the segment including at least one interrogation position complementary to a corresponding nucleotide in the reference sequence (Figure 3),

(2) second, third and fourth probe sets, each comprising a corresponding probe for each probe in the first probe set, the probes in the second, third and fourth probe sets being identical to a sequence comprising the corresponding probe from the first probe set or a subsequence of at least six nucleotides thereof that includes the at least one interrogation position, except that the at least one interrogation position is occupied by a different nucleotide in each of the four corresponding probes from the four probe sets (Figures 3, 7, 8 and 9 and Claim 28).

Skiena in view of Futreal et al. further in view of Cantor et al. do not teach a method wherein the sequence of the target nucleic acid is estimated by :

a) comparing the relative specific binding of four corresponding probes from the first, second, third and fourth probe sets ;

b) assigning a nucleotide in the sequence of the target nucleic acid as the complement of the interrogation position of the probe having the greatest specific binding ;

Cronin et al. teach a method wherein the sequence of the target nucleic acid is estimated by :

a) comparing the relative specific binding of four corresponding probes from the first,

second, third and fourth probe sets (Column 164, claim 28, lines 51-53);

b) assigning a nucleotide in the sequence of the target nucleic acid as the complement of the interrogation position of the probe having the greatest specific binding (Column 164, claim 28, lines 54-56);

Skiena in view of Futreal et al. do not teach a method wherein the sequence of the target nucleic acid differs from the reference by at least two positions within a probe length.

Cronin et al. teach a method wherein the sequence of the target nucleic acid differs from the reference by at least two positions within a probe length (Column 35, lines 1-6).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine and substitute the sequencing of whole human genome study of Cronin et al. in the method of Skiena in view of Futreal et al. further in view of Cantor et al., since Cronin et al. state, "The invention provides several strategies employing immobilized arrays of probes for comparing a reference sequence of known sequence with a target sequence showing substantial similarity with the reference sequence, but differing in the presence of , e.g., mutations (Column 2, lines 8-12)." An ordinary practitioner would have been motivated to combine and substitute the sequencing of whole human genome study of Cronin et al. in the method of Skiena in view of Futreal et al. further in view of Cantor et al. in order to achieve the express advantages noted by Cronin et al. of a method which provides several strategies employing immobilized arrays of probes for comparing a reference sequence of known sequence with a target sequence showing substantial similarity with the reference sequence, but differing in the presence of , e.g., mutations.

4. Claims 3 and 4 are rejected under 35 U.S.C. 103 (a) over Skiena (U.S. Patent 5,683,881) (November 4, 1997) in view of Futreal et al. (U.S. Patent 6,045,997) (April 4, 2000) further in

view of Cantor et al. (U.S. Patent 5,795,714) (August 18, 1998) further in view of Horwitz et al. (Journal of Virology, (1992), Vol. 66 (4), pages 2170-2179).

Skiena in view of Futreal et al. further in view of Cantor et al. teach method of claims 1, 2, 5-6 and 15 and as described above.

Skiena in view of Futreal et al. further in view of Cantor et al. do not teach method wherein the target nucleic acid sequence is a species variant of the reference sequence and wherein the reference sequence is from a human and the target nucleic acid is from a primate.

Horwitz et al teach method wherein the target nucleic acid sequence is a species variant of the reference sequence and wherein the reference sequence is from a human and the target nucleic acid is from a primate (Abstract and Figures 1 and 3).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to include the comparative primate versus human gene sequence study of Horwitz et al. in the method of Skiena in view of Futreal et al. further in view of Cantor et al., since Horwitz et al. state, "Because of the recent identification of several classes of human endogenous retroviruses and our interest in obtaining a better understanding of the evolution of human immunodeficiency virus (HIV), experiments were performed to detect the presence of HIV-1 related sequences in normal human DNA (Page 2170, column 2, second paragraph, lines 1-6)." An ordinary practitioner would have been motivated to combine the comparative primate versus human gene sequence study of Horwitz et al. in the method of Skiena in view of Futreal et al. further in view of Cantor et al. in order to achieve the express advantages noted by Horwitz et al. of obtaining a better understanding of the evolution of human immunodeficiency virus (HIV).

Response to Arguments

5. Applicant's arguments with respect to all pending claims have been considered but are they are not persuasive.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Applicant also argues that there is no motivation to combine the references. This argument is not persuasive, especially in the presence of strong motivation provided by Futreal et al. since Futreal et al. state, "Such oligonucleotide probes or primers, as well as the full length sequence (and alleles, variants and derivatives) are also useful in screening a test sample containing a nucleic acid for the presence of alleles and variants, especially those that confer susceptibility or predisposition to cancers, the probes hybridizing with a target sequence from a sample obtained from the individual being tested. The conditions of the hybridization can be controlled to minimize non-specific binding, and preferably stringent to moderately stringent hybridization conditions are preferred. The skilled person is readily able to design such probes, label them and devise suitable conditions for hybridization reactions, assisted by textbooks such as Sambrook et al and ausubel et al. As well as determining the presence of polymorphisms or mutations in the BRCA2 sequence, the probes may also be used to determine whether mRNA encoding BRCA2 is present in a cell or tissue (Column 9, lines 4-21)." Same logic is applicable to other references as well.

Applicant argues that the examiner is not merely interpreting the claims broadly, but effectively reading out explicitly recited claim steps of "estimating the sequence". This argument

is not persuasive. Skiena inherently teaches both steps of hybridization and estimating the sequence of a target nucleic acid (Column 9, lines 33-49, and Column 4, lines 19-21).

Applicant also argues that Skiena does not teach "estimating" or "reestimating" a target sequence. This argument is not persuasive. Skiena clearly teaches "estimating" or "reestimating" a target sequence (Column 9, lines 33-49, and Column 4, lines 19-21).

Applicant also argues that Cantor does not teach "design of an array to analyze a target sequence that is variant of a known gene". This argument is not persuasive. Cantor clearly teaches "design of an array to analyze a target sequence that is variant of a known gene" (Example 13). Moreover Cronin et al teaches the same design as Cronin et al. state, "The invention provides several strategies employing immobilized arrays of probes for comparing a reference sequence of known sequence with a target sequence showing substantial similarity with the reference sequence, but differing in the presence of , e.g., mutations (Column 2, lines 8-12)."

In view of the response to argument, all previous rejections are hereby maintained properly.

Conclusion

6. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR

1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Arun Chakrabarti, Ph.D. whose telephone number is (703) 306-5818. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion, can be reached on (703) 308-1119.Any inquiry of a general nature or relating to the status of this application should be directed to the Group analyst Chantae Dessau whose telephone number is (703) 605-1237. Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission via the P.T.O. Fax Center located In Crystal Mall 1. The CM1 Fax Center numbers for Technology Center 1600 are either (703) 305-3014 or (703) 308-4242. Please note that the faxing of such papers must conform with the Notice to Comply published In the Official Gazette, 1096 OG 30 (November 15, 1989).

Arun Chakrabarti

Patent Examiner

Art Unit 1634

March 24, 2003

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